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Colobomatous Microphthalmia, Microcephaly With Cerebellar Hypoplasia: Association or New Syndrome?

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We report on a 3.5-year-old girl with microcephaly, microphthalmia, coloboma of the iris, mild developmental delay, and other minor anomalies. Neuroimaging showed marked cerebellar and vermian hypoplasia. This condition has not been described previously and is discussed in the context of the "micro syndrome," together with other similar syndromes. Our case highlights the heterogeneity of the "microphthalmia plus brain malformations" group of patients. Am. J. Med. Genet. 92:278–280, 2000.
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INTRODUCTION

Microphthalmia occurs in many syndromes, most of them without severe mental retardation. A small proportion of patients with microphthalmia have other findings including microcephaly and gross brain malformations demonstrable with modern neuroimaging methods. Warburg et al. described a family with microphthalmia and brain malformations largely restricted to agenesis or hypoplasia of the corpus callosum, which was termed the "micro syndrome" [Mégarbané et al., 1999a; Warburg et al., 1993]. There have been at least five other reports describing one or more patients with microphthalmia with documented brain malformations [Mégarbané et al., 1999a,b; Ozkinay et al., 1997; Seemanová and Lesny, 1996; Siber, 1984]. In all of these cases, the brain malformations involved callosal agenesis or hypoplasia, and in several pedigrees appeared to be X-linked. We now describe a girl with colobomatous microphthalmia, microcephaly, and cerebellar hypoplasia and propose that this case be viewed as prototypic of a new syndrome.

CLINICAL REPORT

This Sicilian girl was born at term to a 29-year-old primagravid mother after an uncomplicated pregnancy. The parents were first cousins. Birth weight was 2750 g and length was 48 cm, appropriate for gestational age. At birth she was noted to be microcephalic, with head circumference (OFC) of 31.5 cm, and also to have iris coloboma, microphthalmia, cataracts, and other anomalies at the anterior and posterior chambers. A CT scan performed at 12 months for possible developmental delay showed bilateral optic nerve hypoplasia, enlargement of the fourth ventricle, and marked cerebellar hypoplasia.

At 17 months she was able to sit unsupported, but unable to stand or walk without support. Her verbal output was limited to several consonant-vowel combinations but no true words. No specific diagnostic tests were ordered.

She was first hospitalized at the Pediatric Neurology Clinic at the University of Catania at age 3.5 years. Her weight was 12 kg and length 92 cm, at the 3rd and 10th centiles, respectively. She was still markedly microcephalic with OFC 47 cm (<3 centile). In addition to microphthalmia, cataracts, and coloboma she had high arched palate, ptosis, flat nasal bridge, triangular facies, joint laxity, incurved fifth fingers, and optic atrophy without retinal pigmentary changes (Fig.1). There was no history of deafness or seizures. She was able to walk short distances with assistance, say her name, recite the alphabet, and speak spontaneously.

Her neurological examination was notable for severely reduced visual acuity with intact light perception. Her eye movements were not roving, but she had marked nystagmus on end-gaze. Her facial movements were normal, as were movements of the tongue and palate. Muscle tone, bulk, and strength were judged to be normal, and no adventitious movements were noted. She sat with titubation but had minimal evidence of dysdiadochokinesis. There was a suspicion of dysmet-

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Fig. 1. The proposita at present age of 3.5 years. Note the flat nasal bridge, bilateral ptosis, and triangular faces.

ria based on the quality of her movements, but this could not be formally tested due to inadequate vision. Her gait was mildly ataxic and performed on a somewhat wide base. She seemed to grope for support as she attempted to walk.

Results of laboratory studies including hemogram, hemoglobin electrophoresis, serum protein electrophoresis, thyroid function panel, routine chemistries, and plasma lead were normal. Plasma and urine amino acids, urine organic acids, lactate/pyruvate, ceruloplasmin, very long-chain fatty acids, and alpha-fetoprotein were all normal. Titers for toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus were absent. Chest radiograph, full skeletal survey, and abdominal ultrasound findings were normal. Chromosomes with high resolution (high-resolution G and R banding) were normal (46,XX).

EEG showed diffuse increase in beta activity possibly due to sedation. Brainstem auditory evoked responses and audiometry were normal, but visual evoked responses were markedly attenuated bilaterally, consistent with prechiasmatic dysfunction. Brain MRI (Fig. 2A) showed mild dilatation of the fourth ventricle with marked cerebellar hypoplasia, particularly involving the vermis. Brainstem was normal and failed to show evidence of the so-called "molar tooth" sign [Maria et al., 1999; Satran et al., 1999] seen in other syndromes with cerebellar hypoplasia. Other brain structures, including the corpus callosum, were normal. MRI also demonstrated microphthalmia (Fig. 2B).

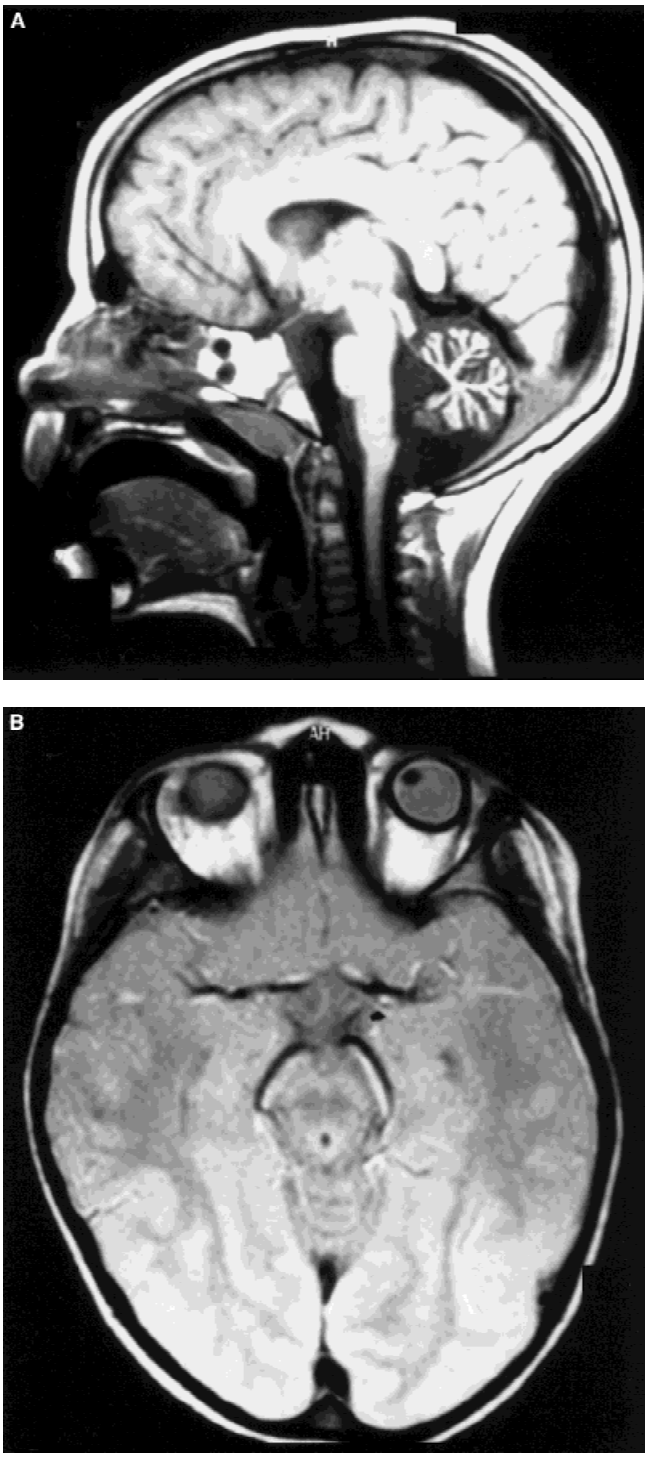

Fig. 2. **A:** Spin-echo head MRI demonstrating marked cerebellar hypoplasia. **B:** MRI showing microphthalmia, slightly more evident in the right eye.

DISCUSSION

Our proposita had multiple anomalies including microcephaly and colobomatous microphthalmia. Subsequent evaluation of the child showed evidence of marked hypoplasia of the cerebellum, particularly the vermis. The patient has cerebellar signs that correlate with the neuroradiologic findings. The child is moderately developmentally delayed, although she clearly has had a nonprogressive course.

Congenital eye malformations are relatively uncommon. Bermejo and Martínez-Frías [1998] found a prevalence of 0.035% among live births of over one million infants studied; other smaller studies suggest a slightly higher rate [Stoll et al., 1997], but still <0.1%. Among children with congenital eye malformations, microphthalmia is relatively common, being seen in approximately half the cases. In contrast, colobomatous microphthalmia, i.e., the combination of coloboma plus

microphthalmia, is quite uncommon, being recorded in only 0.0017% of the live births surveyed by Bermejo and Martínez-Frías [1998].

Structural severe brain malformation is relatively common in patients with microphthalmia or anophthalmia. Among the 243 patients with anophthalmia or microphthalmia, 41 had holoprosencephaly and 3 had anencephaly. Most patients with microphthalmia are not severely mentally retarded, and in these cases, brain malformations are either not present or are less severe. There are several reports of patients with microphthalmia and partial or complete agenesis of the corpus callosum [Mégarbané et al., 1999a; Ozkinay et al., 1997; Warburg et al., 1993]. Microphthalmia with agenesis of the corpus callosum can be seen [Mégarbané et al., 1999a; Ozkinay et al., 1997; Warburg et al., 1993] in the Lenz microphthalmia syndrome (MIM 309800), which is X-linked and thus unlikely to be present in our patient, even as a phenotypic variant. Warburg et al. [1993] have used the term micro syndrome (MIM 600118) to refer to patients with microcornea, microcephaly, congenital cataract, severe mental retardation, and optic nerve atrophy, findings that overlap those seen in this patient. However, all three patients described by Warburg et al. had agenesis of the corpus callosum and cerebellar abnormalities were not described. Recently, Rodriguez Criado et al. [1999] described two sisters with severe mental retardation who had microcephaly, microphthalmia, hypoplasia of the cerebellar vermis, cataracts, and retinal coloboma. However, these patients also had cortical dysplasia and hypoplasia of the corpus callosum, somewhat similar to micro syndrome, but clearly different from our proposita.

Microphthalmia with agenesis of the corpus callosum is also seen in Aicardi syndrome [Aicardi et al., 1969], Goltz syndrome, and the microphthalmia with multiple linear skin defects (MLS) syndrome [Lindsay et al., 1994; Naritomi et al., 1992]. All three of these syndromes appear to be lethal in hemizygous males, and occur exclusively in females. However, our patient had no history of seizures and had nonspecific abnormalities on EEG; also, the coloboma here were of the iris and not the optic nerve, and chorioretinal lacunae were not present. Therefore, there are many findings distinct from those in Aicardi syndrome. This patient lacked the characteristic dermatologic signs seen in Goltz or MLS syndromes, and is therefore difficult to view as a phenotypic variant of those syndromes.

A survey of Online Mendelian Inheritance in Man (OMIM) lists 26 conditions with cerebellar hypoplasia. Of these, only three syndromes (Walker-Warburg, Neu-Laxova, and Meckel) also involve microphthalmia; there are marked differences between our patient's phenotype and any of these three syndromes. A number of patients with Aicardi syndrome have been described with cerebellar hypoplasia and other cerebellar anomalies [Hamano et al., 1989; Serrano and Prats, 1998] at autopsy, but this occurs in the context of more general brain abnormalities. Cerebellar hypoplasia and coloboma of the iris or choroid may also seen in patients with Joubert syndrome and similar syndromes including Arima, Senior-Löken, and COACH syndromes [Satran et al., 1999]; these cases differ in that our patient has prominent microphthalmia, which has not been described in these syndromes. Jung et al. [1995] reported on two unrelated patients with iris coloboma and cerebellar hypoplasia, but these patients also had tracheostenosis, endocrine abnormalities, and dislocated hips. We conclude that our patient is prototypic of a new clinical entity.

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